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EXAMINER	
KINSEY, NICOLE	
ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/700,143	**Applicant(s)** LORENCE ET AL.	
	Examiner Nicole E. Kinsey, Ph.D.	**Art Unit** 1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 August 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,5-19 and 21*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation sheets.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-19 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a carcinoid tumor with a replication-competent, oncolytic strain of Newcastle Disease Virus (NDV), does not reasonably provide enablement for any replication-competent strain of NDV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Scope of enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to a method of treating a carcinoid tumor and carcinoid syndrome by administering a replication-competent NDV to a mammal.

State of the prior art. At the time the invention was made, only certain NDV strains were labeled as "antineoplastic agents" for human tumors (See Sinkovics et al.). In addition, Sinkovics et al. states that "[v]arious NDV strains differ widely in their biological effects including oncolysis and without specific studies of a given NDV strain, generalizations that it is oncolytic just because it is a NDV strain are invalid and

unacceptable." (See Sinkovics et al. entire article, especially page 11). Furthermore, Wildner states, with respect to NDV, that "[s]train differences are substantial in respect to virulence, syncytium formation, replication, immune response, and oncolysis (See Wildner at pages 297-297, Newcastle disease virus heading). In addition, there are replication-competent, **non-oncolytic** strains of NDV (see Cassel et al., Cancer 1965, 18:863-868) where an oncolytic strain (73-T) of NDV was compared to a non-oncolytic strain (20Z) of NDV.

Breadth of the claims. The claims are extremely broad, encompassing treatment of a carcinoid tumor and carcinoid syndrome with any replication-competent NDV, even non-oncolytic strains of NDV.

Working examples. There are only working examples for the oncolytic, mesogenic strain MK107 of NDV.

Guidance in the specification. The specification teaches only the use of the oncolytic, mesogenic strain MK107 of NDV to treat a carcinoid tumor. There is no specific guidance regarding administering to a mammal any replication-competent non-oncolytic NDV strain. Further, the specification does not disclose anti-tumor effects with non-oncolytic strains of NDV.

Predictability of the art. The art with regard to NDV strains being oncolytic is acknowledged to be unpredictable as stated above under the heading *State of the prior art.* In the instant application, Applicants have not disclosed any non-oncolytic strains of NDV that can be utilized in accordance with the invention to treat a mammalian subject having a carcinoid tumor and carcinoid syndrome.

Amount of experimentation necessary. It is not known whether non-oncolytic strains of NDV would have any effect against a carcinoid tumor or carcinoid syndrome.

The claims must be commensurate in scope with the specification and one example is not enabling for the use of the class or genus of replication-competent NDVs. In ex parte Jackson, 217 USPQ 805, even a "description of several newly discovered strains of bacteria having one particularly desirable metabolic property in terms of conventionally measured culture characteristics and number of metabolic and physiological properties does not enable one of ordinary skill in the relevant art to independently discover additional strains having the same specific, desirable metabolic property". The results achieved in the examples are not predictive of the effect of any replication-competent strain of NDV on a carcinoid tumor and carcinoid syndrome as claimed.

Given the breadth of the claims, the lack of guidance in the specification, and the predictability of the art, it would require undue experimentation for one skilled in the art to use the claimed methods.

Response to Arguments

Applicants' arguments filed August 20, 2007 have been fully considered but they are not persuasive. Applicants first argue that the Office has not met its burden of presenting adequate evidence or reasoning to support its doubts as to the anti-tumor activity of non-oncolytic strains of NDV. To support this argument, applicants cite Sinkovics et al. ("Other NDV infections may assume persistent 'carrier culture' formation

(Lawton et al., 1980) in which the infected cell survives, produces complete or incomplete (noninfectious) virions, expresses viral antigens and thus attracts reactions by host antibodies and immune T cells aimed at the destruction of the infected tumor cell.")

According to § 2164.04 of the M.P.E.P., to make an enablement rejection, the examiner has the initial burden to establish a **reasonable** basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure) (emphasis added).

Applicants' specification discloses and discusses replication-competent oncolytic strains of NDV with anti-tumor effects (see, for example, Example I). The specification defines "replication-competent virus" to mean a virus that produces infectious progeny in cancer cells. There is no mention or teaching in the specification that non-oncolytic strains of NDV have anti-tumor effects. In fact, the Office has cited references (see State of the prior art section above). For example, Cassel et al. (Cancer 1965, 18:863-868) compares an oncolytic strain (73-T) of NDV to a non-oncolytic strain (20Z) of NDV. Cassel et al. also states that others (Southam and Moore) showed no anti-tumor effects with a non-oncolytic strain of NDV (see page 867). Thus, the initial burden to establish a reasonable basis to question the enablement has been met.

As for applicants citation of Sinkovics et al. ("Other NDV infections may assume persistent 'carrier culture' formation (Lawton et al., 1980) in which the infected cell

survives, produces complete or incomplete (noninfectious) virions, expresses viral antigens and thus attracts reactions by host antibodies and immune T cells aimed at the destruction of the infected tumor cell."), the quoted text states other NDV strains **may** assume persistent carrier culture formation. This quote is part of a much larger paragraph where the authors question and postulate about different characteristics and biological features of NDVs. This quote in no way provides evidence that non-oncolytic strains of NDV have anti-tumor effects.

Next applicants argue that the non-oncolytic La Sota strain of NDV has anti-tumor effects. Applicants support this argument by citing Krishnamurthy et al. ("We then examined four other strains of NDV (Kansas, California, La Sota, and Australian-Victoria) to see how they replicate and grow in the HT-1080 and CCD-1122Sk cell lines (Table 2). The strains were infected at a low multiplicity (MOI 0.001), and the characteristics of their infections were compared with those of the 73-T strain. We observed that the growth of these strains in normal and tumor cells was comparable to that of the 73-T strain. Thus, different strains of NDV are inherently tumor selective and may be equally useful as anti-tumor therapeutic agents.") This argument, too, is not found persuasive.

The cited quote relates solely to NDV growth in normal cells versus tumor cells. Growth in tumor cells does not translate into anti-tumor abilities. There are strains of NDV that selectively grow on tumor cells versus non-tumor cells but do not cause cell lysis. For example, NDV strain 20Z (discussed above) grows on tumor cells (not non-

tumor cells) but is not oncolytic and does not show anti-tumor properties (see Cassel et al., Discussion).

Given the breadth of the claims, insufficient guidance in the specification, no working examples showing anti-tumor effects with nonlytic strains of NDV, and the state of the art (see discussion above), it would require undue experimentation for one skilled in the art to practice the claimed methods.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5-8 and 16-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 7, 19, 22-25 and 27 of US Patent No. 7,056,689 ("the '698 patent"). Although the

conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating cancer in a mammal by administering a negative-stranded RNA virus (NDV). The '689 claims are drawn to treating a subject having a tumor with NDV. The '689 claims include treating a subject who may or may not have carcinoid syndrome (all that is required is that the subject has a tumor). Therefore, the scope of the '689 claims encompasses treating a subject with a carcinoid tumor and carcinoid syndrome.

Claims 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 157-161, 163-170, 172, 174, 183, 196-219, and 230-232 of copending Application No. 09/958,809. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to infecting a tumor in a mammal with a virus comprising administering to said mammal an RNA virus, wherein said virus is administered as a first dose and one or more subsequent doses, and wherein the first dose is a desensitizing dose, to thereby infect said tumor (Treating a tumor in a mammal with an oncolytic virus will, at the same time, infect the tumor). The copending claims are drawn to infecting a tumor with an interferon-sensitive, replication competent RNA virus. The copending claims include infecting a tumor in a subject who may or may not have carcinoid syndrome. Therefore, the scope of the copending claims encompasses infecting a tumor in a subject who has a carcinoid tumor and carcinoid syndrome.

Claims 1, 5-8, 13, 16, and 17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-8, 50, 51, 63-65, 69, 70, 73, 115-120, 132, 134, 136, and 144 of copending Application No. 10/167652 ("the '652 application"). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating cancer by administering a replication competent, interferon sensitive clonal RNA virus to a mammal. The carcinoid tumor of the instant application is within the breadth of the term neoplasm, which is recited in the '652 application claims (see claims 7, 50 and 51). In addition, treating a neoplasm or tumor in a mammal with a virus will, at the same time, infect the neoplasm or tumor. Further, the copending claims include infecting a tumor in a subject who may or may not have carcinoid syndrome. Therefore, the scope of the copending claims encompasses infecting a tumor in a subject who has a carcinoid tumor and carcinoid syndrome.

Claims 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 12, 17, 21, 22, 26-28 and 34 of copending Application No. 10/518,732 ("the '732 application"). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to administering a therapeutic negative-stranded RNA virus to a subject in one or more cycles, wherein at least one cycle comprises administering sequentially one or more desensitization doses of the

virus followed by administering one or more escalated doses of the virus, wherein the amount of the virus in each of the one or more escalated doses is higher than the amount of virus in each of the desensitization doses. Although claims 13-15 of the instant application do not recite "the amount of the virus in the second and any subsequent desensitization dose is not less than the amount of the virus in the preceding desensitization dose," the scope of the '732 claims overlaps with claims 13-15 of the instant application.

Claims 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/547,654 ("the '654 application"). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to administering a therapeutic negative-stranded RNA virus to a subject in one or more cycles, wherein at least one cycle comprises administering sequentially one or more desensitization doses of the virus followed by administering one or more escalated doses of the virus, wherein the amount of the virus in each escalated dose is higher than the amount of virus in each desensitization dose. Although claims 13-15 of the instant application do not recite a time period between the desensitizing dose and the escalated dose or a rate for administration, the scope of the '654 claims overlaps with claims 13-15 of the instant application.

Claims 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 10/548,057 ("the '057 application"). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to administering a therapeutic negative-stranded RNA virus to a subject in one or more cycles, wherein at least one cycle comprises administering sequentially one or more desensitization/initial doses of the virus followed by administering one or more escalated/subsequent doses of the virus, wherein the amount of the virus in each escalated dose is higher than the amount of virus in each desensitization dose.

Claims 1, 5-8 and 16-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14, 17, 18, 21, 22, 33, 34, 36-39, and 41 of copending Application No. 11/441,201. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating cancer or a tumor by administering to a mammal a negative-stranded RNA virus. The copending claims are drawn to treating a subject having a tumor with NDV. The copending claims include infecting a tumor in a subject who may or may not have carcinoid syndrome. Therefore, the scope of the copending claims encompasses infecting a tumor in a subject who has a carcinoid tumor and carcinoid syndrome.

Response to Arguments

One of ordinary skill in the art would have reasonably expected some patients to have one or more symptoms of carcinoid syndrome such as cancer-related pain or edema (both of which are known symptoms of carcinoid tumors and carcinoid syndrome). Therefore, practicing the methods in the cited and copending applications to treat subjects with carcinoid tumors using Newcastle Disease Virus is reasonably expected to have also treated at least one symptom of carcinoid syndrome.

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nicole E. Kinsey, Ph.D. whose telephone number is (571) 272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nicole E. Kinsey, Ph.D.
Examiner
Art Unit 1648

/Stacy B. Chen/ 9-7-07
Primary Examiner, TC1600